"This is a copy of a presentation from the 41st Congress of the European Committee for Treatment and Research of Multiple Sclerosis and the 30th Conference of Rehabilitation in Multiple Sclerosis, which was in Spain; the references to "Merck" or "Merck KGaA" within refer to (1) Merck KGaA, Darmstadt, Germany; (2) an affiliate of Merck KGaA, Darmstadt, Germany; or (3) one of the businesses of Merck KGaA, Darmstadt, Germany, which operate as EMD Serono in the healthcare, MilliporeSigma in the life science and EMD Electronics in the electronics business in the U.S. and Canada.

There are two different, unaffiliated companies that use the name "Merck". Merck KGaA, Darmstadt, Germany, which is providing this content, uses the firm name "Merck KGaA, Darmstadt, Germany" and the business names EMD Serono in the healthcare, MilliporeSigma in the life science and EMD Electronics in the electronics business in the U.S. and Canada. The other company, Merck & Co., Inc. holds the rights in the trademark "Merck" in the U.S. and Canada. Merck & Co., Inc. is not affiliated with or related to Merck KGaA, Darmstadt, Germany, which owns the "Merck" trademark in all other countries of the world."

The Effect of Cladribine Tablets on Brain Volume Over 4 Years in the MAGNIFY-MS Extension Study

Frederik Barkhof, Klaus Schmierer, Patrick Vermersch, Heinz Wiendl, Xavier Montalban, Anat Achiron, Tobias Derfuss, Andrew Chan, Alexandre Prat, Letizia Leocani, Finn Sellebjerg, Suzanne Hodgkinson, *Muriel Danten, Lidia Gardner*, Nicola De Stefano

This work was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945). Authors in italics are employees of Merck or its affiliates. Please scan the QR code below for full affiliations.

SCAN FOR POSTER PDF

RESEARCH IN CONTEXT

1. **Cladribine tablets preserved brain volume long-term in people with multiple sclerosis, with changes remaining below pathological thresholds regardless of prior therapy.**
2. **Short-course treatment with cladribine tablets delivers durable peripheral and central effects in people with multiple sclerosis, without chronic immunosuppression, supporting long-term cognitive health.[1–4]**

OBJECTIVES

To assess the long-term effect of cladribine tablets on brain volume changes in people with multiple sclerosis (PwMS).

INTRODUCTION

Excessive brain atrophy (EBA) is a predictor of disease progression and worsening physical disability in PwMS.[5] Pathological brain volume loss has been attributed to an annual change of -0.4% or more.[6]

Cladribine tablets have demonstrated both peripheral and central anti-inflammatory effects to promote a more homeostatic and less pathogenic immune environment in PwMS.[1,3]

Previous data have demonstrated reduced brain atrophy over 2 years in PwMS following initiation of cladribine tablets, with stability or improvement in cognitive function.[4,7] This 4-year analysis of the MAGNIFY-MS (NCT03364036) and MAGNIFY-MS Extension (NCT04783935) studies aims to evaluate long-term evidence.

METHODS

- A total of 219 PwMS entered MAGNIFY-MS Extension (female, 64.8%; mean age ± standard deviation [SD], 40.4 ± 9.5 years; treatment (Tx)-naïve, n=89; Tx-experienced, n=130; **Supplementary Table 1**).
- Cladribine tablets were given in two short courses over 2 years, per label.
- Imaging scans were taken at regular intervals over 4 years and analysed using the SIENA-XL method. Brain volume data were re-baselined at month (M) 6 to account for pseudoatrophy.[8]
- The threshold for EBA at M24 and M48 was defined as annualised percentage brain volume change (aPBVC) of –0.4% or more.[6]
- Clinical outcomes were compared for groups with and without EBA at M48. Statistics are descriptive.

Clinical outcomes evaluated by M48 EBA status

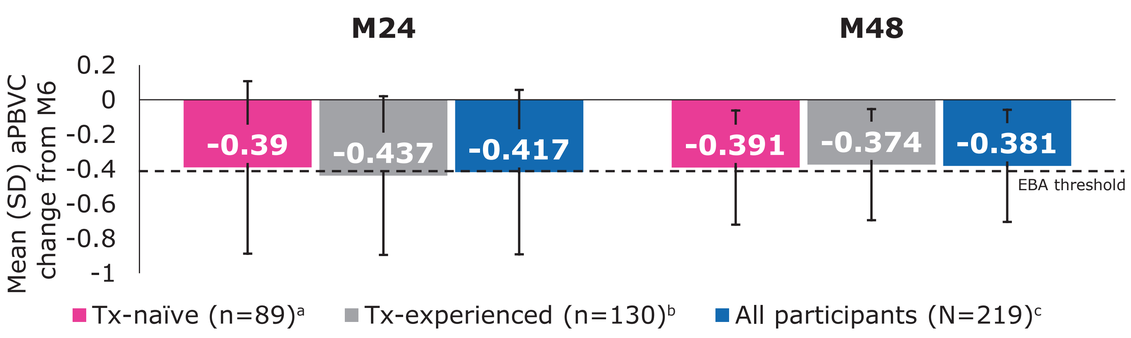
Outcome	Definition
Change in EDSS score	A change in EDSS score from baseline of ≤-1, -0.5 (improved), 0 (stable), 0.5, ≥1 (worsened)
ARR	ARR at M48
Mobility worsening	≥20% worsening in T25FW or 9HPT score from baseline
PIRA	6M-CDP (based on EDSS[a]) with no relapse within 90 days of the event[b]
RAW	Any other 6M-CDP event that did not qualify for PIRA[b]
CDA	Any PIRA or RAW event[b]

[a]Increased EDSS: ≥1.5 points from BL EDSS 0; ≥1 point from BL EDSS 0.5–4.5; or ≥0.5 points from BL EDSS ≥5. [b]Probability estimated with Kaplan-Meier method.
6M-CDP, 6-month confirmed disability progression; **9HPT**, 9-hole peg test; **ARR**, annualised relapse rate; **BL**, baseline; **CDA**, confirmed disability accumulation; **EBA**, excessive brain atrophy; **EDSS**, Expanded Disability Status Scale; **M**, month; **PIRA**, progression independent of relapse activity; **RAW**, relapse-associated worsening; **T25FW**, timed 25-foot walk

RESULTS

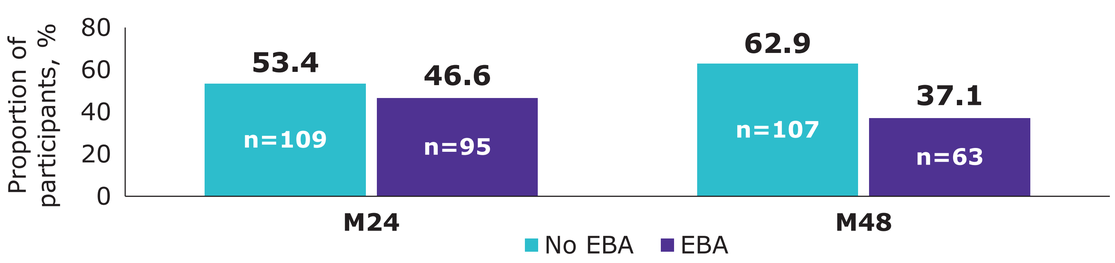
- Four years after the first treatment dose, aPBVC was below 0.4% and was similar for both Tx-naïve and Tx-experienced PwMS (**Figure 1**).

Figure 1. Mean Annual BV Decrease at M48 Was Less Than 0.4% Regardless of Treatment History



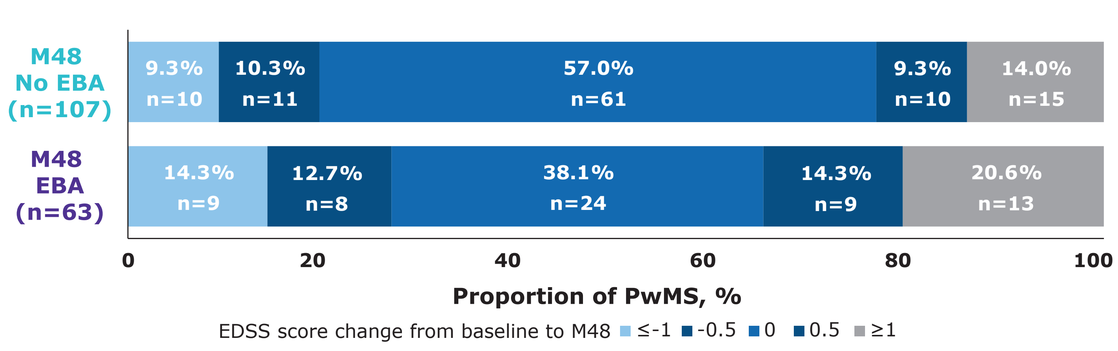
Brain volume data were re-baselined at M6 to account for pseudoatrophy.
[a]Missing: M24, n=3; M48, n=18. [b]Missing: M24, n=12; M48, n=31. [c]Missing: M24, n=15; M48, n=49.
aPBVC, annualised percentage brain volume change; **BV**, brain volume; **M**, month; **SD**, standard deviation; **Tx**, treatment

Figure 2. Most Participants Did Not Exhibit EBA



Based on participants with evaluable data. Missing: M24, n=15; M48, n=49.
EBA, excessive brain atrophy; **M**, month

Figure 3. The Proportion of PwMS With Stable EDSS Score at M48 Was Greater for PwMS With No EBA



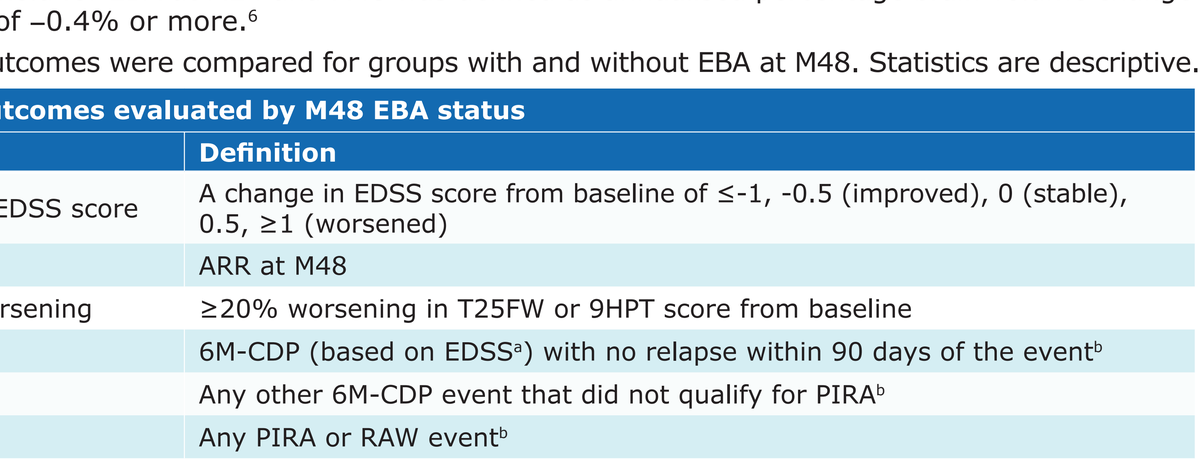
Based on participants with evaluable data (N=170).
EBA, excessive brain atrophy; **EDSS**, Expanded Disability Status Scale; **M**, month; **PwMS**, people with multiple sclerosis

- For both the EBA and no EBA groups, the proportion of PwMS with stable or improved EDSS was more than 60%, but the proportion was greater in the no EBA group (**Figure 3**).

Relapse rate

- At M48, PwMS with no EBA had a lower annualised relapse rate (mean ± SD, 0.043 ± 0.12) compared with the EBA group (0.155 ± 0.26).

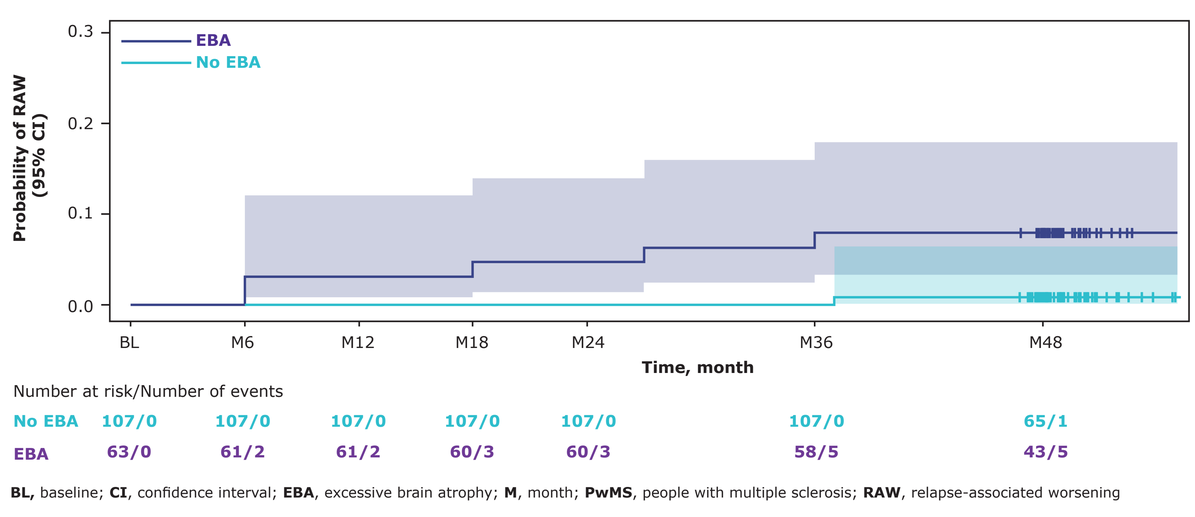
Figure 4. Most PwMS With No EBA Had No Worsening in T25FW Score at M48



[a]PwMS with EBA: T25FW missing, n=2 (3.2%); 9HPT missing, n=1 (1.6%).
9HPT, 9-hole peg test; **EBA**, excessive brain atrophy; **M**, month; **PwMS**, people with multiple sclerosis; **T25FW**, timed 25-foot walk

- At M48, a larger proportion of PwMS in the no EBA group compared with the EBA group had no worsening in T25FW score, whereas the proportion of PwMS with no worsening in 9HPT score was similar between the groups (**Figure 4**).

Figure 5. The Probability of RAW Was Lower in PwMS with no EBA Over 48 Months



BL, baseline; **CI**, confidence interval; **EBA**, excessive brain atrophy; **M**, month; **PwMS**, people with multiple sclerosis; **RAW**, relapse-associated worsening

- Probability of RAW at M48 was much lower for PwMS in the no EBA group (0.9 [95% confidence interval (CI): 0.1, 6.4]) than EBA PwMS (7.9 [95% CI: 3.4, 18.0]; **Figure 5**).
- PIRA probability was <8% in both groups. CDA probability was slightly lower in the no EBA group (8.4%) versus the EBA group (12.7%; **Supplementary Table 2**).

CONCLUSIONS

- **In PwMS treated with cladribine tablets, mean aPBVC was less than 0.4% in years 2–4 during the treatment-free period, regardless of treatment history, demonstrating sustained preservation of brain volume.**
- **At M48, the no EBA group had markedly lower ARR, clinical worsening, and disability accumulation than the EBA group.**
  - **PwMS with EBA had higher probabilities of increased EDSS score, RAW, and CDA.**
- **These findings highlight the importance of brain volume preservation as a therapeutic goal in multiple sclerosis.**

SCAN FOR AFFILIATIONS, DISCLOSURES, AND SUPPLEMENTARY MATERIALS

References: 1. Wiendl H, et al. *Front Immunol*. 2025;16:1512189. 2. Oreja-Guevara C, et al. *Mult Scler Relat Disord*. 2023;69:104459. 3. Schmierer K, et al. *Ther Adv Neurol Disord*. 2025;18:17562864251351760. 4. De Stefano N, et al. *Eur J Neurol*. 2025;32(S1):e70191 (EPR-275). 5. Rojas JI, et al. *Arq Neuropsiquiatr*. 2016;74:235-243. 6. De Stefano N, et al. *J Neurol Neurosurg Psychiatry*. 2016;87:93–99. 7. Achiron A, et al. *Mult Scler*. 2025:13524585251313749. 8. Sastre-Garriga J, et al. *Nat Rev Neurol*. 2020;16:171–182.

Presented at ECTRIMS 2025 | 24–26 September | Barcelona, Spain

Supplementary Materials:

Supplementary Table 1. Participant Demographics and Characteristics

	Tx-naïve (n=89)	Tx-experienced (n=130)	All participants (N=219)
Female, n (%)[a]	54 (60.7)	88 (67.7)	142 (64.8)
Age at baseline, years, mean ± SD[a]	36.2 ± 9.2	38.2 ± 9.5	37.4 ± 9.4
Age at MAGNIFY-MS Extension informed consent, years, mean ± SD	39.3 ± 9.2	41.2 ± 9.6	40.4 ± 9.5
Time since onset of MS, months, median[a]	15.8	78.2	53.8
Number of relapses within 12 months prior to baseline, n (%)[a]			
0	0	2 (1.5)	2 (0.9)
1	13 (14.6)	78 (60.0)	91 (41.6)
2	58 (65.2)	45 (34.6)	103 (47.0)
>2	18 (20.2)	5 (3.8)	23 (10.5)
EDSS score at baseline			
Median (Q1; Q3)	2.0 (1.5; 3.0)	2.0 (1.5; 3.0)	2.0 (1.5; 3.0)
>3, n (%)[a]	19 (21.3)	32 (24.6)	51 (23.3)
Number of previous DMTs, n (%)[a]			
0	89 (100.0)	0	89 (40.6)
1	0	76 (58.5)	76 (34.7)
2	0	40 (30.8)	40 (18.3)
>2	0	14 (10.8)	14 (6.4)
Presence of any T1 Gd+ lesions, n (%)[b]	44 (49.4)	66 (50.8)	110 (50.2)
Presence of any active T2 lesions, n (%)[b]	34 (38.2)	60 (46.2)	94 (42.9)
Nonevaluable	2 (2.2)	0	2 (0.9)

[a]Data recorded at MAGNIFY-MS parent study baseline. [b]Data recorded at MAGNIFY-MS baseline period (defined as the time between the screening visit and the baseline visit in MAGNIFY-MS; median period, 36.0 [range, 21–91] days).
DMT, disease-modifying therapy; **EDSS**, Expanded Disability Status Scale; **Gd+**, gadolinium-enhancing; **MS**, multiple sclerosis; **Q**, quartile; **SD**, standard deviation; **Tx**, treatment

Supplementary Table 2. Probability of PIRA, RAW, and CDA at M48

KM estimate at M48 (95% CI)	No EBA (n=107)	EBA (n=63)
PIRA	7.5 (3.8, 14.4)	6.3 (2.4, 16.0)
RAW	0.9 (0.1, 6.4)	7.9 (3.4, 18.0)
CDA	8.4 (4.5, 15.5)	12.7 (6.6, 23.8)

CDA, confirmed disability accumulation; **CI**, confidence interval; **EBA**, excessive brain atrophy; **M**, month; **PIRA**, progression independent of release activity; **RAW**, relapse-associated worsening

Supplementary Materials:

Author Affiliations:

Frederik Barkhof,[1,2] Klaus Schmierer,[3,4] Patrick Vermersch,[5] Heinz Wiendl,[6] Xavier Montalban,[7] Anat Achiron,[8,9] Tobias Derfuss,[10] Andrew Chan,[11] Alexandre Prat,[12] Letizia Leocani,[13-15] Finn Sellebjerg,[16,17] Suzanne Hodgkinson,[18] Muriel Danten,[19] Lidia Gardner,[20] Nicola De Stefano[21]

[1]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands; [2]Queen Square Institute of Neurology and Centre for Medical Image Computing, University College London, London, UK; [3]The Blizard Institute, Centre for Neuroscience, Surgery and Trauma, Faculty of Medicine & Dentistry, Queen Mary University of London, London, UK; [4]Clinical Board Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, UK; [5]Université deLille, Inserm U1172 LilNCog, CHU Lille, FHU Precise, Lille, France; [6]Department of Neurology and Neurophysiology, Medical Center – University of Freiburg, Freiburg, Germany; [7]Department of Neurology/Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), Hospital Universitario Vall d'Hebron, Barcelona, Spain; [8]Multiple Sclerosis Center, Sheba Academic Medical Center, Ramat Gan, Israel; [9]Faculty of Medicine, Tel-Aviv University, Israel; [10]Department of Neurology, University Hospital Basel, Basel, Switzerland; [11]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [12]Department of Neurosciences, Université de Montréal, Montréal, QC, Canada; [13]University Vita-Salute San Raffaele, Milan, Italy; [14]Scientific Institute IRCCS San Raffaele, Milan, Italy; [15]Department of Neurorehabilitation Science, Casa di Cura Igea, Milan, Italy; [16]Danish MS Center, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Glostrup, Denmark; [17]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [18]Ingham Institute for Applied Medical Research, University of New South Wales Medicine and Liverpool Hospital, Sydney, NSW, Australia; [19]Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA; [20]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA; [21]Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

Author Disclosures:

FB is supported by the NIHR Biomedical Research Centre at UCLH and is a steering committee or data safety monitoring board member for ATRI/ACTC, Biogen, Merck, and Prothena. He is a consultant for Celltrion, Combinostics, IXICO, Janssen (J&J), Merck, Rewind Therapeutics, and Roche. Research agreements with Biogen, GE Healthcare, Merck, and Roche. Co-founder and shareholder of Queen Square Analytics Ltd.

KS receives research support from the National Institute for Health and Care Research, Biogen, Merck, Novartis, Roche, Sandoz, and Sanofi; speaking honoraria from, and/or served in an advisory role for, Biogen, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Merck, Neuraxpharm, Novartis, Roche, and Sanofi; and remuneration for teaching activities from AcadeMe and Medscape.

PV has received honoraria or consulting fees from AB Science, Ad Scientiam, Biogen, Celgene (Bristol Myers Squibb), Imcyse, Janssen (J&J), Merck, Novartis, Roche, Sanofi, and Teva; and research support from Novartis, Roche, and Sanofi.

HW receives research support from Deutsche Forschungsgemeinschaft (DFG), Deutsche Myasthenie Gesellschaft e.V., European Union, Alexion, Amicus Therapeutics Inc., Argenx, Biogen, CSL Behring, F. Hoffmann-La Roche, Genzyme, Merck, Novartis, Roche, and UCB Biopharma, as well as speaker and/or consultancy fees from Alexion, Argenx, Argobio, AOCN, AstraZeneca, BGP Products Operations GmbH, Biogen, Bristol Myers Squibb, CEMCAT, Dianthus, EMD Serono Research & Development Institute, Inc., Billerica, Ma, USA, an affiliate of Merck KGaA, EPG Health/Medthority, Fondazione Cariplo, Genzyme, Idorsia, Immunic, Immunovant, INmune Bio_Syneos Health, Kohlhammer, LTS, Lundbeck, Merck, MS at the Limits, Muna Therapeutics, Myrobalan Therapeutics, Neurodiem, NMSS, Novartis, Ology, PSL Group, Red Nucleus, Roche, Samsung, Sangamo, Sanofi, Springer, StreamedUp, Swiss MS Society, Teladochealth, Toleranzia, Teva, UCB, Uvet, Viatris, and WebMD global. He is a member of scientific advisory boards from Alexion, Argenx, Biocryst, Bristol Myers Squibb, Cellerys, Galapagos, Janssen, Merck, Novartis, Sandoz-Hexal, and uniQure biopharma B.V.

XM's institution has received compensation for lecture honoraria and travel expenses, participation in scientific meetings, clinical trial steering committee membership, or clinical advisory board participation in recent years from Abbvie, Actelion, Alexion, AstraZeneca, Autolus, Bial PD, Biogen, Bristol Myers Squibb/Celgene, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Genzyme, Hoffmann-La Roche, Immunic Therapeutics, Indivi, Janssen Pharmaceuticals, Juvisé Pharmaceutical, Lilly, MedDay, Medscape, Merck, Mylan-Viatris, NervGen, Neuraxpharm, Novartis, PeerVoice, Rewind Therapeutics, Samsung-Biosys, Sandoz, Sanofi-Genzyme, Teva Pharmaceutical, TG Therapeutics, Zenas Biopharma, EXCEMED, ECTRIMS, MSIF, and NMSS or any of their affiliates.

AA has received, over the last 5 years, honoraria or consulting fees for participating in advisory boards related to clinical trial design, trial steering committees, and data and safety monitoring committees from Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, and Sanofi; and research support for investigator-initiated trials and MS patients' benefits activities from Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, and Sanofi.

TD serves on scientific advisory boards for Actelion (Janssen/J&J), Bayer, Biogen, Celgene (Bristol Myers Squibb), GeNeuro, MedDay, Merck, Mitsubishi Pharma, Novartis, Roche, and Sanofi; has received funding for travel and/or speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi; and receives research support from Actelion, the European Union, Novartis, Roche, the Swiss MS Society, and the Swiss National Foundation.

AC has received speakers'/board honoraria from Actelion (Janssen/J&J), Almirall, Bayer, Biogen, Celgene (Bristol Myers Squibb), Merck, Novartis, Roche, Sanofi, and Teva, all for hospital research funds. He received research support from Biogen, Sanofi, and UCB, the European Union, and the Swiss National Foundation. He serves as associate editor of the *European Journal of Neurology*, on the editorial board for *Clinical and Translational Neuroscience*, and as topic editor for the *Journal of International Medical Research*.

AP has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years, and/or received operating grants from Alexion, Bayer, Biogen, Celgene (Bristol Myers Squibb), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Novartis, Roche, Sanofi, and Teva.

LL has received honoraria for consulting services or speaking activities from Merck and Roche.

FS has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, Celgene (Bristol Myers Squibb), EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA, Merck, Novartis, Roche, Sanofi, and Teva.

SH serves on advisory boards for Bayer, Biogen, Merck, Novartis, Roche, and Sanofi. She has received money for travel and speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi.

MD is an employee of Merck Santé S.A.S., Lyon, France, an affiliate of Merck KGaA.

LG is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA.

NDS has received honoraria from Biogen-Idec, Bristol Myers Squibb, Celgene, Genzyme, Immunic, Merck, Novartis, Roche, and Teva for consulting services, speaking, and travel support. He serves on advisory boards for Immunic, Merck, Novartis, Biogen-Idec, Roche, and Sanofi. He has received research support from the Italian Ministry of University and Research and Fondazione Italiana Sclerosi Multipla. He is associate editor of *Neurological Sciences* and co-founder of Siena-Imaging s.r.l.

Acknowledgements:

The authors would like to thank all the study participants, family members, and staff from all sites that were involved in the study.

Joe Ward of Springer Health+, Springer Healthcare Ltd., UK, provided medical writing support, which was funded and supported by Merck in accordance with the Good Publication Practice 2022 Guidelines.